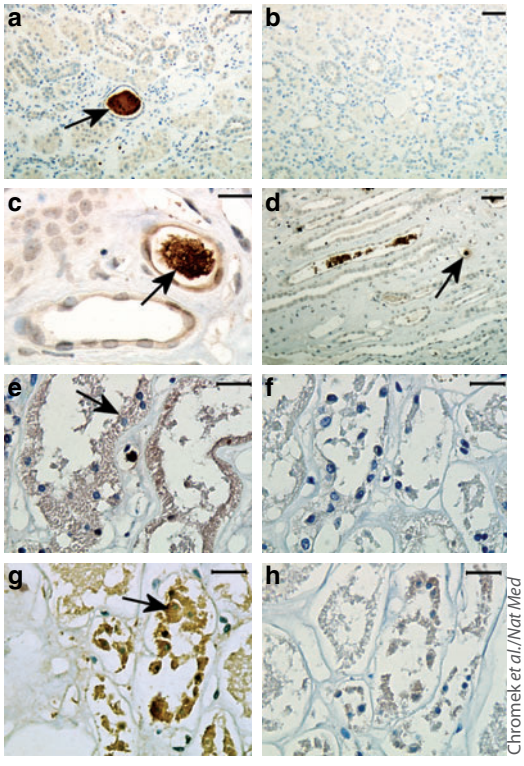
Kidney International (2006) **70**, 622–623. doi:10.1038/sj.ki.5001782

The antimicrobial peptide cathelicidin is responsible for ensuring sterility of urine

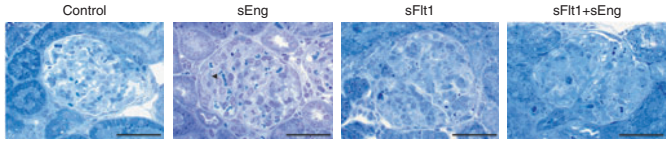
Many processes allow the urinary tract to remain bacteria free, including urine flow rate, rapid bladder emptying, and the mounting of an active inflammatory response by white blood cells. Recent studies have demonstrated that many epithelia secrete antimicrobial peptides whose function is to ensure mucosal sterility. These peptides belong to two families, defensins and cathelicidins. Defensins and cathelicidins are expressed in neutrophils as well. In a recent paper, Chromek *et al.* found that the urinary tracts of mice and humans produce the cathelicidins LL-37 and cathelin-related antimicrobial peptide (CRAMP). These peptides (human and murine, respectively) are produced as longer propeptides and cleaved to form the active C-terminal cathelicidin. The proteins and their precursors were present in the lumen of the tubules. When sections of normal kidneys were exposed to uropathogenic *Escherichia coli*, the expression of cathelicidins in the tubular epithelial cytoplasm increased. Contact of epithelial cells with the bacterium resulted in its release into urine. Purified cathelicidin killed uropathogenic *E. coli in vitro*. In a mouse model of UTI, *E. coli.* were injected into the bladder, and their attachment to the mucosa was evaluated 1 hour later — before neutrophil invasion occurred. Animals deficient in cathelicidin had more bacteria attached than wild-type animals. They also had more severe signs of systemic infection, such as loss of weight, than wild-type animals. In addition, clinical *E. coli* strains isolated from patients with more severe urinary tract infections (pyelonephritis) were more resistant to cathelicidin killing than strains isolated from patients suffering from cystitis. Thus, cathelicidin seems to be a key factor in mucosal immunity of the urinary tract. (*Nat Med* 2006; **12**: 636–641)

Qais Al-Awqati



Immunohistochemical staining of sections from healthy human renal cortical tissue (**a**–**d**), a piece of human renal cortex incubated in cell culture medium for 24 hours (**e** and **f**), and a piece infected with uropathogenic *E. coli* for the same time (**g** and **h**). Scale bars, 50 µm (**a**,**b** and **d**); 20 µm (**c**,**e**,**f**,**g** and **h**).

Soluble endoglin contributes to the pathogenesis of preeclampsia



Venkatesha *et al./Nat Med*

Renal, histological changes in pregnant rats after sEng and sFlt1 treatment. Arrowhead: mild focal endotheliosis. Scale bars, 50 µm.

Preeclampsia is characterized by hypertension and proteinuria in the third trimester of pregnancy. The placenta has a central role in preeclampsia, as evidenced by rapid disappearance of the disease symptoms after delivery. The clinical manifestations of preeclampsia reflect widespread endothelial dysfunction, resulting in vasoconstriction, end-organ ischemia, and increased vascular permeability. Therefore, it has long been suspected that a placenta-derived circulating factor(s) may induce the endothelial defects, leading to preeclampsia. Previous work has suggested that high levels of circulating soluble fms-like tyrosine kinase (sFlt1, also known as soluble VEGF receptor 1) of placental origin probably contribute to the pathogenesis of preeclampsia. Overexpression of sFlt1 in rats led to hypertension, proteinuria, and glomerular endotheliosis. sFlt1-treated animals, however, did not develop hemolysis and thrombocytopenia, complications observed in severe preeclampsia. A recent study by Venkatesha *et al.* postulates that other placenta-derived soluble factors may act in concert with sFlt1 to cause endothelial dysfunction, resulting in severe preeclampsia. Endoglin (Eng), or CD105, a cell surface coreceptor for transforming growth factor-β1 (TGF-β1) and TGF-β3 isoforms, is highly expressed in endothelial cells and syncytiotrophoblasts and modulates actions of TGF-β1 and TGF-β3. The authors found that Eng localized to caveolae, where it was associated with endothelial nitric oxide synthase (eNOS)

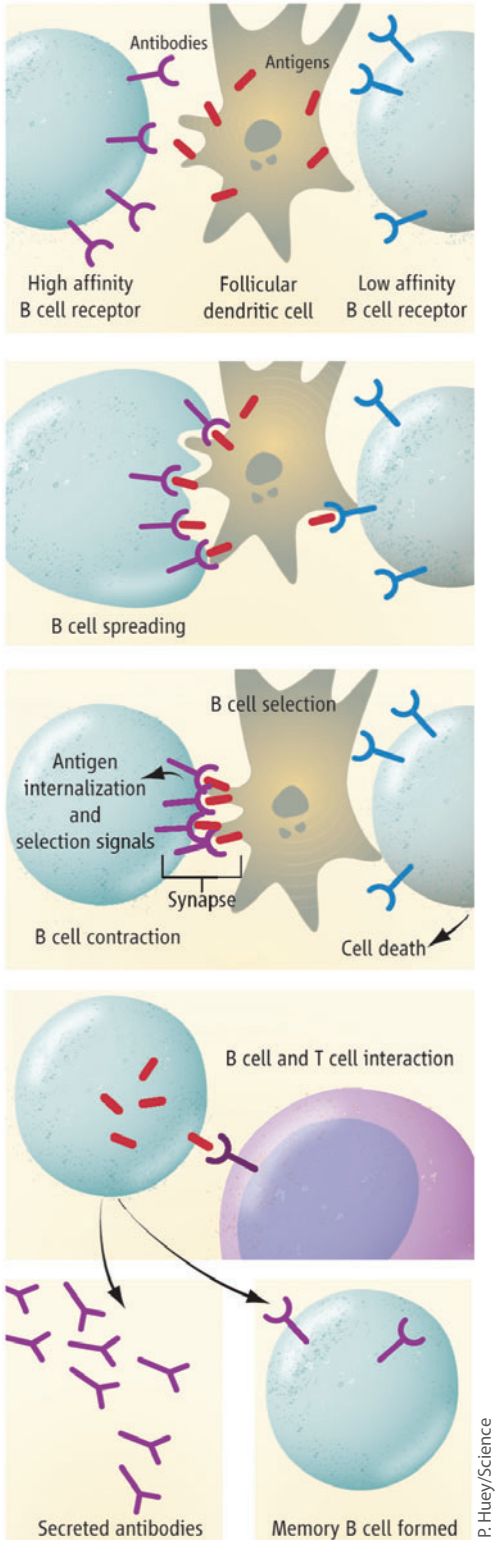
and regulated its activity and local vascular tone, suggesting that Eng is involved in vascular homeostasis. They also identified a novel placenta-derived soluble TGF-β coreceptor, soluble endoglin (sEng), which was elevated in the sera of preeclamptic individuals and whose levels correlated with disease severity. sEng inhibited formation of capillary tubes *in vitro* and induced vascular permeability and hypertension *in vivo*. Its effects in pregnant rats were amplified by coadministration of sFlt1 (Figure), leading to preeclampsia and its more severe form, the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. sEng impaired binding of TGF-β1 to its receptors and downstream signaling, including effects on activation of eNOS and vasodilation, suggesting that sEng leads to dysregulated TGF-β signaling in the vasculature. These results demonstrate that sEng may act in concert with sFlt1 to induce severe preeclampsia. (*Nat Med* 2006; **12**: 642–649)

Juan Oliver

How B cells spread and gather

B lymphocytes play an important role in the immune response to infection, secreting neutralizing antibodies to combat invading pathogens. Using sophisticated imaging and mathematical modeling, Batista and colleagues explain how in the early stages of the selection process B cells dynamically spread and contract over cell membranes that bear antigen (either anchored in the membrane or tethered to the membrane as an immune complex).[1] A perspective by Margaret Harnett discusses this mechanism (Figure).[2] This process allows the B-cell receptor to differentially sense antigens of widely varying affinities by the amount of antigen acquired, which dictates the level of B-cell activation. In their initial findings, Batista and colleagues showed that B-cell receptor recognition of antigens tethered to the membrane led to the formation of an immunological synapse. By internalizing the B-cell receptor–antigen complex, B cells acquired antigens from target cells. This process enhanced the activation of B cells at low antigen concentration and affinity, thereby potentiating (by several orders of magnitude relative to soluble antigen) subsequent antigen processing and presentation to T cells. The study also showed that the integrin molecule LFA-1, which has been implicated in the interaction of B cells with follicular dendritic cells, worked with VLA-4 to form a region called the peripheral supramolecular activation cluster (pSMAC) that surrounds the central cluster of B-cell receptor–antigen (cSMAC). This suggests that B cells can form mature immunological synapses. Although in the initial stages of the immune response B cells are likely to respond in such a way to antigen via low-affinity receptors, somatic mutation in the germinal centers generates high-affinity B-cell receptors that are selected by competitive binding to antigen tethered to follicular dendritic cells in the form of immune complexes. Therefore, unlike T cells that recognize antigen through low-affinity interactions, B cells sense and differentiate a wide range of affinities *in vivo*. The gathering of antigen by B cells occurs without adhesion molecules or compromising the fundamental features of the antigen-specific responses. In this regard, Batista and colleagues clarify the powerful discriminatory ability of B cells. ([1]*Science* 2006; **312**: 738–741. [2]*Science* 2006; **312**: 709–710)

Marc De Broe



B-cell discrimination of antigen affinity can dictate cell fate.